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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/839,194	02/20/92	GORDON	K IG5-4.4

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EXAMINER	
CROUCH, D	
ART UNIT	PAPER NUMBER
1632	21

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Offic Action Summary

Application No.	Applicant(s)
07/839,194	Gordon et al.
Examiner	**Group Art Unit**
Deborah Crouch	1632

☒ Responsive to communication(s) filed on *Oct 28, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1, 2, 4-9, 11, and 16-29* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 4-9, 11, and 16-29* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Applicant's arguments filed October 28, 1999 have been fully considered but they are not persuasive. The amendment has been entered. However, the claims added numbered 12-25, have been renumbered 16-29. Caneled claim numbers are not available for use in new claims. Claims 12-15 were original claims canceled in the amendment filed February 20, 1992. Thus, claims 1,2,4-9,11 and 16-29 are pending.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1,4-9,11 and 16-29 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1,3-9,11and 16-29 of copending Application No. 08/927,936. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Claims 1,4-9,11 and 16-29 of the instant application are stated to be a DNA construct. Claims 1,4-9,11 and 16-29 are stated to be a sequence. However, there is no difference between these terms, and between the claims, as the elements of the DNA construct and the DNA sequence are identicial. Futher the DNA construct of the instnat claims is composed of the DNA sequence of '936. Both sets of claims anticipate each other. As there is no patentable distinction, they are rejected as under the statutory double patenting provision above.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 2 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,2,4-9,11 and 16-29 of copending Application No. 08/927,936. Although the conflicting claims are not identical, they are not patentably distinct from each other because the cleavage of a secretory signal sequence is an inherent property of producing a protein with a signal sequence. As part of the post-translational machinery in the mammary gland cell, the signal sequence of each of claims 1,2,4-9,11 and 16-29 in '936 are cleaved. As such, the specfic step of cleavage in claim 2 of the instant application is obvious over claims 1,2,4-9,11 and 16-29 of '936.

Claims 1,2,4-9,11,16,19-21 and 24-29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 24 of copending Application No. 08/246,259. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 1,2,4-9,11,16,19-21 and 24-29 are drawn to DNA constructs where the construct comprises a gene encoding a protein under the regulation of a milk protein promoter sequence which does not naturally control transcription of the gene and where the DNA construct also comprises secretory signal sequence. In '259, the specification defines gene encoding a protein as being a gene encoding tPA, HbSAg; and WAP as being a milk protein, and more specifically as a milk serum protein promoter (see specification, page 2, lines 5-15; page 3, line 22 - page 5, line 8; and page 6, lines 5-11). The specification further defines the secretory signal sequence as being between the gene and the promoter, as being either naturally associated with the protein encoded by the gene, or as being naturally associated with the milk protein (see specification page 6, line 12 - page 7, line 5). The specification defines the construct as having a transcriptional stop sequence from SV40, and more specificially the SV40 polyadenylation sequence (specification, page 7, lines 10-15). Therefore, instant claims 1,2,4-9,11,16,19-21 and 24-29 are obvious over claim 24 of '259 as the embodiments of claims

1,2,4-9,11,16,19-21 and 24-29 are contained within claim 24 of '259. Given claim 24, the ordianry artisan at the time of the instant invention would have had a reasonable expectation of success in implementing claims 1,2,4-9,11,16,19-21 and 24-29. Applicant is reminded that the specification is available in an obviousness-type double patenting rejection to define the terms of the claims.

These are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Claims 1,2,5-9,11 and 16-29 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The specification provides only a description of one mammalian serum milk protein promoter, and that is the WAP promoter in ATCC Accession No. 67032. There is no description of any other WAP promoter or other mammalian milk serum protein promoter such that at the time of filing, 1986, it is evident that applicant had possession for the breadth of the claimed invention. Furthermore, the disclosure does not describe mammalian serum milk promoters for their breadth such that their structure could be envision by the skilled artisan at the time of filing.

The Written Description Guidelines argued by the Examiner are those published in December 1999 (Fed. Reg., Vol. 64, No. 244, Tuesday, December 21, 1999, pages 71427-71440).

Applicant argues that genus of milk proteins is very small, including approximately a dozen proteins.

Applicant argues that the claimed invention is not a new gene of new genetic entity purified from nature, but a combination of known art elements. Applicant argues that the specification goes beyond naming the elements and is not merely a wish, or means of isolating the element.

Applicant argues that the art taught the structure and thus the naming of promoter and its gene is sufficient.

Applicant argues that the Guidelines for Written Description have been mis-applied and do not have relevance here as they are not claiming a novel nucleic acid sequence.

Applicant argues that the instant fact pattern is the polar opposite of that in *University of California V. Eli Lily,* 43 USPQ2d 1398. Applicant argues, in view of *University of California V. Eli Lily,* that the specification teaches milk protein promoters are to be used in constructs of the inventions. Applicant argues that they do not need to recite specific casein promoters because the genus of casein promoters is so small. Applicant argues that it is accepted that the naming of a generic term having a small number of species constitutes sufficient written description of the species. In support, applicant cites *Bigham v. Godtfredsen,* 8 USPQ2d 1266. Applicant argues that under *University of California v. Eli Lily* and the Guidelines there is written description when the promoter sequences were known in the art at the time of filing. Applicant argues that their sequences were known in the art at the time of filing.

These arguments are not persuasive.

While the number of milk protein gene promoters is small, there still needs to be adequate description of them to convey to the public that the inventor had possession of them at the time of filing. Issue is taken with applicant's statements that milk protein gene promoters were known in the art at the time of filing. As discussed at length in the enablement rejection, the art at the time of filing at most knew the sequence of the 5' flanking sequence of several milk protein genes, but no analysis had been performed to identify promoter sequences. The knowledge of the 5' flanking sequence and some regions similar to promoter regions of other genes does not convey possession of promoter sequences for milk protein genes. No structure is given for promoter sequences when they are presumed to be embedded in a 5' flanking region, which can be hundreds or thousands of base pairs in length. The holding in *Bigham v. Godtfredsen* states "in the case of a small and closely related group such as the halogens, the naming of the group should ordinarily be sufficient since nothing of consequence would be added by also naming each of the well known members of the group". The milk protein gene promoter sequences are only functionally related in that they regulate expression, but little if anything is known of their specific regulation and whether or not the regulation of expression is responsive to exactly the same factors at the

same time. However, there is no evidence that they are structurally related at all such that the WAP sequence would provide description of the others. With distinct promoter sequences, consequential information would be provided with knowledge of the sequences involved. Further, there is no comparison with the well known halogens with any group of promoters. Halogens have been studied for years, if not for a full century. Milk protein promoter sequences in no fashion had had at the time of filing the same extensive study as halogens. Thus, the holdings in *Bigham v. Godtfredsen* are not seen as relevant to the instant fact pattern.

As for the holding in *University of California v. Eli Lily*, there are no teachings in the Guidelines that these holdings are only to be applied in DNA sequence claims. As the claimed invention requires very specific promoter sequences it is only reasonable that they would fall under the written description guidelines and the holdings of *University of California v. Eli Lily*. The physical structure of the promoters is essential to the invention and describing them by function is not sufficient to provide the artisan with knowledge of them or that the inventor had possession of them at the time of filing. Milk protein gene promoters certainly tells what the promoters do, but it does not tell the nucleic acid sequence so that the written description requirement is met. Critical, essential elements to a claim must meet the written description criteria of 35 U.S.C. 112, first paragraph. In summary, possession of "milk protein promoters" by the inventor has not been shown because there is only a functional description of such promoters, with any accompanying structural description, and the promoters had not been identified by the art at the time of filing. The Guidelines published 12/21/99 are supportive of this analysis (Fed. Reg. 64, page 71435, col. 3, parag. 1).

Claims 1,2,5-9,11 and 16-29 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA constructs containing a gene encoding a protein, said gene being under transcriptional control of a WAP promoter, does not reasonably provide enablement for the breadth DNA constructs containing a gene encoding a protein, said gene being under transcriptional control of mammalian milk serum protein promoters for reasons of record. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. While the claims encompass an enormous number of nucleotide sequences, the specification only teaches a single WAP promoter DNA sequence. The specification provides no guidance as to DNA sequences, fragments of known DNA sequences or assays for determining milk serum protein promoter activity for the breadth of claim. It is well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). In not providing rudimentary guidance in the isolation of the genus "milk serum protein promoters', the specification does not enable the breadth of the claims. The identification of a single milk serum protein promoter DNA sequence is not sufficient enablement for Applicant's broadly claimed invention. Accordingly, as the specification provides insufficient guidance and "experiments in genetic engineering produce, at best, unpredictable results" (*Ex parte Forman*, 230 USPQ 546 (BPAI 1986)), it would have required one of skill in the art undue experimentation to prepare all milk serum protein promoters without a predictable degree of success.

Furthermore, the courts have stated that specifications are required to provide sufficient teachings and guidance to enable the skilled artisan to implement the invention as claimed. For example, *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1005 (CAFC 1997) (emphasis added) states:

> .... a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies*, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Thus in view of this holding, the lack of guidance in the specification as state above to provide guidance as to the methods for isolating milk serum protein promoters for their breadth, the specification is not seen as enabling, and that at the time of filing the skilled artisan would need to engage in an undue amount of experimentation without a predictable degree of success to implement the claimed invention for its breadth.

The declaration by Dr. Gordon is not persuasive as it is not clear, if the WAP promoter used to produce transgenic mice expressing tPA (parag. 6) is the same as that in the disclosed species in ATCC Accession No. 67032. If it is not, then this would lend to the broadening of the scope of enablement regarding the promoter. With regards to the breadth of "mammalian milk serum protein promoters", the only reference is to Dr. Gordon's comment in parag. 3, that she disagrees with the examiner's evaluation of the guidance in the specification. In view of case law of record now, more that a mere statement of disagreement is needed. Applicant should show where in the specification such guidance is given and how the skilled artisan at the time of filing would use such guidance to reach the claimed invention. While there is no doubt to the enablement of the very specific mouse of the declaration, there is a lack of guidance for the breadth of the claimed invention.

In the Appeal Brief filed June 29, 1994, applicant argues that the genomic sequence for α-lactalbumin was known in the art at the time of filing. However, the mere knowledge of a genomic sequence does not put in the hands of the public the promoter sequence(s). Such a disclosure constitutes an invitation to invent. This is especially the situation in view of the case law cited in this office action. While inventors are encouraged by the patent system to disclose early, those disclosures must be enabled and contain adequate written descriptions of the inventions such that the public is given adequate guidance to make and use the invention.

Applicant argues that promoter sequences for milk protein genes were known in the art at the time of filing and thus need not be included in the specification. In support applicant cites Yu-Lee et al. (1986); Campbell et al; Qasba et al.; Jones et al.; Yu-Lee et al (1983) and Stewart et al. Applicant argues that at pages 3 and 4 of the specification, they have provided mammalian milk protein promoters which

can be used in the instant invention. Applicant argues that they have disclosed signal and termination sequences which can be used in the claimed DNA construct. Applicant argues that they have provided methods of making the claimed DNA construct and have disclosed that the exemplified genes encoding tPA and HbSAg can be removed for others to be inserted. Applicant argues that the exemplified WAP promoter can also be removed and exchanged foe another milk protein promoter. Applicant argues that methods for such exchanges within a DNA construct were given in Manniatis et (1982). Applicant argues that as evidence of knowledge in the art at the time of the effective filing date, they refer to the First Declaration of Katherine Gordon. In support applicant refers to Hammer et al. and Kraemer et al. Applicant argues that the Second Declaration of Katherine Gordon demonstrates that procedures to produce transgenic animal expressing a protein of interest in their milk were disclosed in the specification. In support applicant refers to Gordon et al (1987) and Gordon et al (1991). These arguments are not persuasive.

The key issue is whether or not at the time of filing the specification provided sufficient guidance to the artisan to make and use the invention for the breadth of the claims. It is maintained that the instant specification fails to provide guidance as to milk protein promoter sequences for the entire breadth of the genus. It is noted that the WAP promoter is considered to be sufficiently enabled that a scope for this promoter has been given. Further, as the examiner did not raise issues concerning secretory sequences or transcription terminiation codons in the previous office action, these arguments are not addressed. Once the scope of promoter is agreed to these two components of the DNA construct will not be an issue.

The cited art by applicant does not support the argument that milk protein promoters were known at the time of filing as none had been isolated and characterized. Yu-Lee et al (1986) compare the 5'-flanking sequences of rat α, β and γ-casein genes (page 1894, figure 6), but never show any isolated sequences that exhibit promoter activity, nor does Yu-Lee et al (1986) teach any promoter sequences, per se. A comparison of the 5'-flanking sequence is not seen as sufficient to provide guidance to the promoter region contained therein. On pages 1887-1888, there is a discussion of the conservation of sequence between the 5' flanking regions of the rat α-casein and the bovine αS1-casein genes. Again, this does not

disclose promoter regions or promoter sequences for either of these genes. Campbell et al discuss the comparison of rat and mouse whey acidic protein genes. Campbell et al is not relevant given the scope rejection above. Qasba et al compare the sequence of the 5' flanking regions of rat α-lactalbumin and chicken lysozyme genes, and disclose the sequence of a rat α-lactalbumin gene (page 378). However. Qasba et al provide no guidance on those portions of the 5' flanking region which have promoter activity. Qasba et al state that the sequences found in the 5' flanking region are similar too, but not the same as consensus sequences found at initiation sites of other genes and not the same as consensus sequences for progesterone receptor recognition site of the ovalbumin gene (page 379, col. 2, parag. 1). Jones et al discuss the fine structure mapping of the rat β-casein gene, and propose sites of expression regulatory sequences, this is not considered enabling as no such promoter sequences were analyzed for such regulatory activity (page 7043, col. 2, parag. 1 and 2). These regions are referred to by Jones et al as "candidates for regulatory elements". Yu-Lee et al (1983) analyzes the rat γ-casein gene much as Jones et al did for the rat β-casein gene. Yu-Lee et al (1983) does not teach promoter sequences, but only points to proposed sites within the 5' flanking region of the γ-casein gene (page 10798, parag. 1 to page 10799, line 7). Yu-Lee et al (1986) states that a "possible Goldberg-Hogness box" is present in the 5' flanking sequence of the rat γ-casein gene. Stewart et al teach only a comparison of the sequence between a bovine αS1-casein gene and a rat α-casein gene (page 3898). While a regulatory control sequences are suggested by Stewart et al by sequence comparison, there is no definitive identification of promoter sequences from either of these genes. The art cited by applicant to reflect the knowledge at the time of the effective filing date clearly demonstrates that while the sequence of 5' flanking regions of milk protein genes were known, and their flanking regions suggested, there was no clear enablement of such promoter sequences. As the specification provides no additional guidance, save for WAP promoter sequences, the specification is seen as an invitation for applicant to invent. Milk protein gene promoter sequences are an essential, critical element to the implementation of the claimed invention. Critical, essential elements for an invention are to be provided for in the specification such that they are available to the public from a reproducible source. The art cited by applicant and the instant disclosure do not provide such availability.

Until the promoter sequences are available, there can be no simple substitution of one of these promoters for the WAP promoter as argued by applicant in the production of nucleic acid constructs for use in the claimed invention.

It is additionally argued that Gordon declarations I and II do not support applicant's allegations of enablement for the breadth of the claims. Gordon I discusses the production of transgenic animals. However, there is no showing of animals that express a gene encoding a protein of interest in the animal's milk. This is the crux of the invention. While transgenic non-human mammals could have been made at the time of the effective filing date, the issue is whether for the breadth of claims, could the methods of producing a protein of interest in a transgenic mammal's milk have been made. Hammer et al do not answer this question, as they never targeted mammary gland or proposed the production of a protein of interest in the milk of a transgenic non-human mammal. Kraemer et al also offer no guidance to the claimed invention. The calves described merely contain the HSV-tk gene, and do not express any protein in their milk. Neither Hammer et al or Kraemer et al discuss, disclose or enable milk protein gene promoter sequences. The issue is not knowledge of making a transgenic non-human mammal. The rejection is the availability of milk protein gene promoters for the breadth of applicant's claimed invention. As for Gordon declaration II, the only milk protein gene promoter disclosed or discussed is the WAP promoter. This is the same situation for Gordon et al (1987) and Gordon et al (1991). Both of these post-filing reference disclose the WAP promoter in the production of transgenic non-human mammals that produce tPA or a tPA variant in its milk. These references do not address any aspect of the scope rejection which is to the breadth of milk protein gene promoter sequences.

For these reasons the scope rejection is maintained. Further, the specification, for reasons of record, does not meed the standards set forth in *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1005 (CAFC 1997) (emphasis added) states:

> .... a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies*, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement

> requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Thus in view of this holding, the lack of guidance in the specification as state above to provide guidance as to the methods for isolating milk serum protein promoter sequences for their breadth, the specification is not seen as enabling, and that at the time of filing the skilled artisan would need to engage in an undue amount of experimentation without a predictable degree of success to implement the claimed invention for its breadth.

Claims 1,2,4-9 and 111 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 lacks antecedant basis to claim 1 as claim 1 is to milk proteins and not milk serum proteins.

Claim 11 is confusing as it referes to "said protein" in claim 1. It would be clearer if applciant would state something like "wherein said gene encods human tissue plasminogen activator or hepatitis B surface antigen.

Claims 1 and 19 are to be duplicative. The promoter sequence of claim 1 is "a sequence upstream from the transcriptional start site and contains a promoter sequence" as in claim19.

The claims are free of the prior art. At the time of filing, the prior art did not teach or suggest a DNA construct containing a gene encoding a protein where expression of the gene is regulated by a mammalian milk serum protein promoter, where the promoter does not naturally regulate expression of the gene, and the construct further comprising a DNA sequence encoding a signal peptide.

U.S. Patents 5,476,995; 5366,894 and 5,322,777 are cited as of interest.

Claim 4 would be allowable if written independently and with a proper terminal disclaimer.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

The fax number is (703) 308-4242.

Please note the change in art unit number to Art Unit 1632. Please use this art unit number on all correspondence.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Dr. D. Crouch
February 9, 2000